# **CLAIMS:**

- A peptide derivative peptidomimic having general formula X-CX<sub>1</sub>-NH-AA<sub>1</sub>-CONH-AA<sub>2</sub>
  wherein X is a heterocyclic or unusual amino acid, X<sub>1</sub> is O or H<sub>2</sub> and AA<sub>1</sub> and AA<sub>2</sub> are
  amino acids.
- 2. A peptide derivative according to claim 1 wherein X is a heterocyclic selected from the group consisting of F-moc-3- (2-furyl)-L-alanine, F-3- (3-thienyl)-L-alanine, 4-Fmoc-piperazine-1-yl-acetic acid hydrate, Fmoc-3, 3-diphenyl-L-alanine, 1-Fmoc-azetidine-3-carboxylic acid, Benzimidazolepropionic acid, Fmoc1, 2,3,4 tetrahdroquinoline-3-carboxylic acid, 2-oxo-4-phenyl-3-oxazolidine-acetic acid, 5-Methoxy-2-methyl-3-indole acetic acid and 5-Mercapto-1-terazole acetic acid.
- 3. A peptide derivative according to claim 1 wherein X is an unusual amino acids selected from a group consisting of 5-Hydroxytryptophan, L-Abrine, L-β-homoproline, β-HomoTrp -OH, Homophenylalanine L-β-homotryptophan, L-2-propargyl glycine, 3,3 Diphenylalanine, L-β-Homohydroxyproline and Cyclohexylalanine.
- 4. A peptide derivative according to claim 1 wherein the dipeptide for position AA<sub>1</sub>-AA<sub>2</sub>, is selected from the group consisting of Orn-Pro, Cha-Pro, Ile-Pro, Dap-Pro, Val-Trp, Lys-Pro, Lys-Trp, Orn-Trp, Dap-Trp, Ile-Phe, β-Ala-Pro, Pro-Pro and Cha-Trp.
- 5. A peptide derivative according to claim 1 wherein the derivative represented by general formula X-CX1-NH-AA<sub>1</sub>- CONH-AA<sub>2</sub> is selected from the group consisting of:
  - (a) L-Abrine- Orn-Pro, 3- (3-thienyl)-L-alanine- Orn-Pro, 3- (2-furyl)-L-alanine- Orn-Pro, 2-Benzimidazoleacetic acid- Orn-Pro, 5-Hydroxytrytophan- Orn-Pro, Homotryptophan- Orn-Pro, Homophenyalanine- Orn-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Orn-Pro, Azetidine-3-carboxylic acid- Orn-Pro, Cyclohexylalanine- Orn-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Orn-Pro, 4 piperazine acetic acid- Orn-Pro
  - (b) L-Abrine- Cha-Pro, 3- (3-thienyl)-L-alanine- Cha-Pro, 3- (2-furyl)-L-alanine- Cha-Pro, 2-Benzimidazoleacetic acid- Cha-Pro, 5-Hydroxytrytophan- Cha-Pro, Homotryptophan- Cha-Pro, Homophenyalanine- Cha-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Cha-Pro, Azetidine-3-carboxylic acid-Cha-Pro, Cyclohexylalanine- Cha-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Cha-Pro, 4 piperazine acetic acid- Cha-Pro
  - (c) L-Abrine- Ile-Pro, 3- (3-thienyl)-L-alanine- Ile-Pro, 3- (2-furyl)-L-alanine- Ile-Pro, 2-Benzimidazoleacetic acid- Ile-Pro, 5-Hydroxytrytophan- Ile-Pro, Homotryptophan-

Ile-Pro Homophenyalanine- Ile-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Ile-Pro, Azetidine-3-carboxylic acid- Ile-Pro, Cyclohexylalanine- Ile-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Ile-Pro, 4 -- piperazine acetic acid- Ile-Pro.

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- (d) L-Abrine- Dap-Pro, 3- (3-thienyl)-L-alanine- Dap-Pro, 3- (2-furyl)-L-alanine- Dap-2-Benzimidazoleacetic acid- Dap-Pro, 5-Hydroxytrytophan-Pro, Homotryptophan- Dap-Pro, Homophenyalanine- Dap-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Dap-Pro, Azetidine-3-carboxylic acid- Dap-Pro, Cyclohexylalanine- Dap-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Dap-Pro, 4 piperazine acetic acid- Dap-Pro.
- (e) L-Abrine- Val-Trp, 3- (3-thienyl)-L-alanine- Val-Trp, 3- (2-furyl)-L-alanine- Val-Trp, 2-Benzimidazoleacetic acid-Val-Trp. 5-Hydroxytrytophan-Val-Trp. Homotryptophan- Val-Trp, Homophenyalanine- Val-Trp, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Val-Trp, Azetidine-3-carboxylic acid- Val-Trp, Cyclohexylalanine- Val-Trp, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Val-Trp, 4 piperazine acetic acid- Val-Trp.
- (f) L-Abrine-Lys-Pro, 3- (3-thienyl)-L-alanine-Lys-Pro, 3- (2-furyl)-L-alanine-Lys-Pro, 2-Benzimidazoleacetic acid-Lvs-Pro. 5-Hydroxytrytophan-Homotryptophan-Lys-Pro, Homophenyalanine-Lys-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Lys-Pro, Azetidine-3-carboxylic acid- Lys-Pro. Cyclohexylalanine- Lys-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Lys-Pro, 4 piperazine acetic acid- Lys-Pro.
- (g) L-Abrine- Lys-Trp, 3- (3-thienyl)-L-alanine- Lys-Trp, 3- (2-furyl)-L-alanine- Lys-2-Benzimidazoleacetic acid- Lys-Trp, 5-Hydroxytrytophan- Lys-Trp, Homotryptophan-Homophenyalanine- Lys-Trp, Lys-Trp, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Lys-Trp, Azetidine-3-carboxylic acid- Lys-Trp, Cyclohexylalanine- Lys-Trp, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Lys-Trp, 4 piperazine acetic acid- Lys-Trp.
- (h) L-Abrine- Orn-Trp, 3- (3-thienyl)-L-alanine- Orn-Trp, 3- (2-furyl)-L-alanine- Orn-2-Benzimidazoleacetic acid-Orn-Trp, 5-Hydroxytrytophan-Homotryptophan-Orn-Trp. Homophenyalanine-Om-Trp, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Orn-Trp, Azetidine-3-carboxylic acid- Orn-Trp, Cyclohexylalanine- Orn-Trp, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Orn-Trp, 4 piperazine acetic acid- Orn-Trp.

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- (i) L-Abrine- Dap-Trp, 3- (3-thienyl)-L-alanine- Dap-Trp, 3- (2-furyl)-L-alanine- Dap-Trp, 2-Benzimidazoleacetic acid- Dap-Trp, 5-Hydroxytrytophan- Dap-Trp, Homotryptophan- Dap-Trp, Homophenyalanine- Dap-Trp, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Dap-Trp, Azetidine-3-carboxylic acid- Dap-Trp, Cyclohexylalanine- Dap-Trp, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Dap-Trp, 4 piperazine acetic acid- Dap-Trp.
- (j) L-Abrine- Ile-Phe, 3- (3-thienyl)-L-alanine- Ile-Phe, 3- (2-furyl)-L-alanine- Ile-Phe, 2-Benzimidazoleacetic acid- Ile-Phe, 5-Hydroxytrytophan- Ile-Phe, Homotryptophan- Ile-Phe, Homophenyalanine- Ile-Phe, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Ile-Phe, Azetidine-3-carboxylic acid- Ile-Phe, Cyclohexylalanine- Ile-Phe, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Ile-Phe, 4 piperazine acetic acid- Ile-Phe.
- (k) L-Abrine- β-Ala-Pro, 3- (3-thienyl)-L-alanine- β-Ala-Pro, 3- (2-furyl)-L-alanine- β-Ala-Pro, 2-Benzimidazoleacetic acid- β-Ala-Pro, 5-Hydroxytrytophan- β-Ala-Pro, Homotryptophan- β-Ala-Pro, Homophenyalanine- β-Ala-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- β-Ala-Pro, Azetidine-3-carboxylic acid- β-Ala-Pro, Cyclohexylalanine- β-Ala-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- β-Ala-Pro, 4 piperazine acetic acid- β-Ala-Pro.
- (l) L-Abrine- Pro-Pro, 3- (3-thienyl)-L-alanine- Pro-Pro, 3- (2-furyl)-L-alanine- Pro-Pro, 2-Benzimidazoleacetic acid- Pro-Pro, 5-Hydroxytrytophan- Pro-Pro, Homotryptophan- Pro-Pro, Homophenyalanine- Pro-Pro, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Pro-Pro, Azetidine-3-carboxylic acid- Pro-Pro, Cyclohexylalanine- Pro-Pro, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Pro-Pro, 4 piperazine acetic acid- Pro-Pro.
- (m) L-Abrine- Cha-Trp, 3- (3-thienyl)-L-alanine- Cha-Trp, 3- (2-furyl)-L-alanine- Cha-Trp, 2-Benzimidazoleacetic acid- Cha-Trp, 5-Hydroxytrytophan- Cha-Trp, Homotryptophan- Cha-Trp, Homophenyalanine- Cha-Trp, 1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid- Cha-Trp, Azetidine-3-carboxylic acid- Cha-Trp, Cyclohexylalanine- Cha-Trp, 2-Oxo-4-phenyl-3-oxazolidine acetic acid- Cha-Trp, 4 piperazine acetic acid- Cha-Trp.
- 6. A peptidomimic compound according to claim 1 wherein the compound displays angiotensin converting enzyme (ACE) inhibiting activity.
- A peptidomimic compound according to claim 1 wherein the concentration of the peptidomimic compound for 50% inhibition of ACE activity (IC<sub>50</sub>) ranged from 2 μmole

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to 10 µmole in in-vitro condition using synthetic substrate Hippuryl-Histidyl-Leucine (HHL).

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- 8. A peptidomimic compound according to claim 1 wherein the dose of the synthesized ACE inhibiting peptidomimic compound which effectively blocked angiotensin converting enzyme ranges between 5-8 mg/kg of body weight.
- 9. A process to synthesize peptide derivative peptidomimics comprising
  - (a) coupling ACE inhibiting antihypertensive peptidomimic molecule wherein a heterocyclic or unusual amino acid present at ante-penultimate position is coupled to a dipeptide with amino acids present at ultimate position and penultimate position;
  - (b) synthesising dipeptide on a solid support by coupling and deprotection;
  - (c) coupling the heterocyclic or unusual amino acid to deprotected dipeptide at the N-a terminal of dipeptide;
  - (d) cleaving the synthesized peptidomimic compound of step (c) from solid support followed by purification and characterization:
- 10. A process according to claim 9 wherein the solid support used is selected from polystyrene resins linked with a suitable agent/handles.
- 11. A process according to claim 10 wherein the agent is acid labile and comprises 4hydroxymethylphenoxyacetic acid.
- 12. A process according to claim 10 wherein the agent is hyper acid labile and is selected from the group consisting of 4-hydroxymethyl-3methoxy-phenoxyacetic acid and 2chlorotrityl-2-chloride linker.
- 13. A process according to claim 9 wherein the anchoring of activated C-terminal of the N-\alphaprotected amino acid on to the solid support is carried out by symmetrical anhydrides.
- 14. A process according to claim 9 wherein the anchoring of activated C-terminal of the N-αprotected amino acid on to the solid support is carried out by reactive ester formation using 1-hydroxybenzotriazole. benzotriazolyloxy-tridimethylamino-phosphoniumhexaflourophosphate and benzotriazole-1-yl-oxy-trispyrrolidino-phosphoniunmhexaflourophosphate.
- 15. A process as claimed in claim 9 wherein deprotection of the N-α-protected amino acid is carried out removing flouro-methyl-oxy carbonyl group depending on the compatibility with the linking group on the solid support.

- 16. A process according to claim 9 wherein the cleavage is effected using trofluroacetic acid, acetic acid or trifluroethanol depending upon the linking agent/functional group attached on the solid support and the C terminal functional group desired.
- 17. A process according to claim 9 wherein the purification is carried out by gel permeation method using Sephadex G/LH-20 followed by characterization using techniques of HPLC, MALDI-Tof and LC-MS.
- 18. Use of a peptide derivative peptidomimic having general formula X-CX<sub>1</sub>-NH-AA<sub>1</sub>-CONH-AA<sub>2</sub> wherein X is a heterocyclic or unusual amino acid, X<sub>1</sub> is O or H<sub>2</sub> and AA<sub>1</sub> and AA<sub>2</sub> are amino acids as an angiotensin converting enzyme inhibitor.
- 19 Use according to claim 18 wherein the dose of the synthesized ACE inhibiting peptidomimic compound which effectively blocked angiotensin converting enzyme ranges between 5-8 mg/kg of body weight.
- 20. Method for the inhibition of angiotensin converting enzyme in a subject suffering from hypertension comprising administering a pharmaceutically effective amount of a peptide derivative peptidomimic having general formula X-CX<sub>1</sub>-NH-AA<sub>1</sub>-CONH-AA<sub>2</sub> wherein X is a heterocyclic or unusual amino acid, X<sub>1</sub> is O or H<sub>2</sub> and AA<sub>1</sub> and AA<sub>2</sub> are amino acids to the subject with a pharmaceutically effective carrier.
- 21 Method according to claim 20 wherein the subject is a mammal.
- 22. Method according to claim 20 wherein the subject is a human being.
- 23 Method according to claim 20 wherein dose of the synthesized ACE inhibiting peptidomimic compound which effectively blocked angiotensin converting enzyme ranges between 5-8 mg/kg of body weight.